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My colleagues and I are interested in two aspects of cellular neurobiology. First we are working on mechanisms of neuronal cell injury that might be related to brain damage associated with stroke. For the past decade we have looked into the pathophysiology of glutamate toxicity, since there is now convincing evidence that under conditions of brain ischemia there is excessive accumulation of glutamate in the extracelluar space. We believe that this glutamate, acting on a variety of postsynaptic receptors, causes cell damage and eventually death of neurons. In more recent experiments we have started to focus on additional mechanisms of neuronal injury that cannot be accounted for by overactivation of glutamate receptors. We are starting to look for evidence that programmed death or apoptosis occurs in human brain slices after exposure to diminished glucose and oxygen. We are also examining the physiological properties of neurons after aborted apoptosis. The second line of research focuses on the GABA receptor and a class of drugs, gamma- butyrolactones, which can modulate postsynaptic GABA effects. We have found that different lactones either block or potentiate GABA currents in neurons. We are currently investigating the hypothesis that our lactones act at two separate sites within the GABA receptor/ionophore to produce these different effects. By studying GABA receptors that have been mutated in specific regions we have already been able to isolate the blocking effect of lactones to the picrotoxin site. We are planning to mutate the GABA receptor at other sites in an effort to also discover the regions associated with y-butyrolactone potentiation of GABA currents. We believe that these y- butyrolactones hold promise for the treatment of several neurological diseases including epilepsy and that these cellular experiments may provide the stimulus for the development of novel anticonvulsants in the future. As a result of our interest in the lactones and epilepsy, we have begun a series of pilot experiments to explore the therapeutic potential of moderate cortical cooling for the rapid termination of epileptic bursting.

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